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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,130	12/17/2001	Donna Stevens	2148US	3119

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,130	STEVENS ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed	1652	

-- The MAILING DATE of this communication appears on the cover sh t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *40-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-49 are pending and under consideration in this Office action.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I	Claims 1-39, drawn to an assy method of squalene synthase, classified in Class 435, subclass 25.
Group II	Claims 40-42, drawn to the polypeptide of SEQ ID NO: 6, classified in Class 435, subclass 189.
Group III	Claims 43-49, drawn to nucleic acid encoding the a polypeptide of SEQ ID NO: 6, classified in Class 536, subclasses 23.2.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and II are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the polypeptide of Group II can be utilized in other methods such as in a method to make antibody.

Inventions of Groups I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are not disclosed as capable of use together because the methods of Group I does not utilize the nucleic acid of Group III.

The polypeptide of Group II and the nucleic acid of Group III are independent chemical entities and require different searches in the patent and non-patent literature.

During a telephone conversation with Lura Kiefer on January 9, 2004 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-39. Affirmation of this election must be made by applicant in replying to this Office action. Claims 40-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 30 is dependent on claim 29 which utilizes a plant squalene synthase. Thus, claim 30 does not further limit claim 29.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-28 and 30-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claims 1 and 2 are directed to two different methods, yet they have the same steps, which render the claims indefinite and confusing. For examination purposes only, claim 1 is assumed to be directed to a method of estimating the amount of squalene formed in the reaction, whereas claim 2 is directed to a method of determining the rate of reaction (mol. of squalene/unit time) at a given amount of protein concentration.

(b) The clause "the amount of squalene is correlated to the amount of NADPH consumed" in claims 1, 2 and 16 renders the claims indefinite and confusing. The specification teaches that squalene formation is stoichiometric with NADH, i. e., one mole of squalene formed for each one mole of NADPH consumed, see page 5, last paragraph. The claim is confusing because the word "correlated" does not have to be one to one. Substituting "is correlated" with "corresponds" in both claims 1 and 2 would obviate this rejection.

(c) The last two clauses in claim 16 render the claims indefinite and confusing. When the assay set up as described in the claim and specification, it is impossible for the fluorescent emission to increase over time. One of ordinary skill in the art would expect a decrease in the rate of decrease in fluorescence relative to a control in the case of an inhibitor, whereas a promoter should cause an increase in the rate of decrease in fluorescence relative to a control.

(d) The phrase "wherein the squalene synthase" in claim 30 render the claims indefinite and confusing. It is not clear to this examiner which squalene synthase in claim 29 the phrase is referring to. For examination purposes only, it is assumed that the phrase refers to the "plant squalene synthase".

(e) claims 3-15, 17-28 and 31-34 are included in these rejection because they are dependent on rejected claim and do not cure its deficiencies.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Robinson (U. S. P. 5,589,372) in view Wolf *et al.* (Analytical Biochemistry, Jan. 1991, 192 (1), 78-81), Nakashima *et al.* (Proc. Natl. Acad. Sci. U. S. A., March 1992, 92, 2328-2332), and the state of the art as exemplified by the cited references, and Ciosek *et al.* [J. Biol. Chem. November 1993, 268 (33), 24832-24837].

Robinson teaches the nucleic acid sequences encoding the squalene synthase from *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and human, see Figures 2, 8, and 9, respectively. He teaches that squalene synthase catalyzes the formation of squalene and NADP from 2 molecules from faranecyl pyrophosphate (diphosphate), one molecule of NADPH in the presence of Mg^{+2} ion, see column 3, lines 31-35, as well as the role of the enzyme in the biosynthesis of cholesterol in mammals as well as the biosynthesis of isoprenoid and related compounds in plants and insects. In column 5, lines 38-52, he specifically teaches the many possible benefits of eliminating or limiting the activity of squalene synthase. In addition, he teaches the solubilization of squalene

synthase by removing the trans membrane domain from the C-terminus, see column 10, lines 28-33, and example 7 and Figure 4.

Wolf *et al.* teach an assy for L-glutamic acid decarboxylase by monitoring the increase in the fluorescence of NADPH at 460 nm using excitation wave length of 340 nm formed from a dehydrogenase catalyzed reaction coupled to the decarboxylase catalyzed-reaction, see page 79, left column last paragraph. The important and relevant teaching of Wolf *et al.* is that the oxidation/reduction reaction of NADP/NADPH is accompanied by fluorescence change at 460 nm, and thus, a reaction, which utilizes NADP/NADPH can be monitored by observing the fluorescence change at 460 nm.

Nakashima *et al.* teach the cloning of a gene encoding the squalene synthase from *Arabidopsis thaliana*, see Figure 1 on page 2330, which comprises the amino acid sequence of SEQ ID NO: 6. Also, they teach that squalene synthase is one of the key enzymes in sterol biosynthesis, see the first paragraph after the abstract. In addition, they teach that the C-terminal hydrophobic domain is especially characteristic, because it is likely functions as an anchor in the endoplasmic reticulum membrane, see page 2329, right column, third paragraph from the bottom of the page.

Ciosek *et al.* teach that inhibitors of squalene synthase inhibitors are orally active cholesterol lowering agents *in vivo*, see the title and abstract. Also, they teach a radiometric assay, see page 24833, right column, last paragraph. In addition, they teach that effective inhibitors for squalene synthase in human and rate microsomes, but the inhibitors were substantially less effective in inhibiting the yeast enzyme, see page 24836, right column, second paragraph.

The cited prior art provide one of ordinary skill in the art with motivation to develop high through out put assay for squalene synthase as they teach potential inhibitors for the enzyme are potential cholesterol lowering drugs in mammals as well as having many desirable effects on plants and fungi, see in particular the teaching of Robinson. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to adopt the fluorescence assay developed by Wolf *et al.* to assay squalene synthase and quantify the amount of product. The ordinary skill in the art would have been particularly motivated by the fact that florescence based assays are sensitive, do not utilize radioactive material, and allow the continuous measurement of an entire time course for a reaction. The prior art teaches that one mole of NADPH is consumed for each mole of squalene formed, see for example Robinson. The ordinary skill in the art would have recognized that NADPH is a reactant consumed during the reaction and can be measured and quantified directly by florescence as taught by Wolf *et al.* (excitation at 340 nm, emission at 460 nm). The ordinary skill in the art would have prepared a reaction mixture comprising faranecyl pyrophosphate, molecule of NADPH, Mg^{+2} ion in a buffer contained in a fluorescence cell,

placed the cell in a spectroflouremeter using excitation wave length at 340 nm and monitor the reaction by following the decrease of fluorescence at 460 nm. The reaction mixture is initiated by adding an aliquot of squalene synthase preparation (claims 1 and 2). The fluorometric assay may be followed to the end of the reaction or the reaction may be terminated by several well known methods in the art such as change in pH or heat and compare the reading to a control (claim 3). The assay is a general assay for any squalene synthase including human, fungal or plant that would utilize NADPH in the reduction regardless of its biological source (claim 4 and 5), and is amenable to automation in a drug discovery program to identify compounds that modulate the enzymatic activity (claims 16-18). The squalene synthase activity is assayed with 0.9 mM of NADPH, 0.022 mM faranecyl pyrophosphate and 5 mM of magnesium chloride concentration in neutral pH range between 7-8 using any functional buffer at this pH range such as phosphate or tris/HCl buffer as taught by Ciosek *et al.* It should be noted the concentration of the reactant can be varied as desired by one of ordinary skill in the art (claims 11-15 and 24-28). The squalene synthase taught by Nakashima *et al.* has the entire amino acid sequence of SEQ ID NO: 6 which correspond to residues 1-388 of the sequence in the prior art (claim 6). Thus, it is at least 80%, 85%, 90%, and 95% homologous to SEQ ID NO: 6. It should be noted that the prior art teach a method of identifying the membrane binding domain of squalene synthase and Nakashima *et al.* have specifically identify the membrane binding domain at the C-terminus of *A. Thaliana enzyme*. One of ordinary skill in the art would have been motivated to remove the membrane binding domain by truncation at the C-terminus by well known method to produce a water soluble protein. The resulting polypeptide would be expected to be enzymatically active, and would have been obvious to utilize the method developed by the ordinary skill in the art to assay for its enzymatic activity (claims 7-10). It would have been further obvious to the ordinary skill in the art to use in the assay a water soluble squalene synthase to identify inhibitors to modulate the enzymatic activity in plants as desired (claims 19-23). It would have been further obvious to the ordinary skill in the art to compare the inhibition constant of an inhibitors of squalene synthase from fungus, plant, and mammals in order to obtain a selective inhibitor for a particular organism as taught by Ciosek *et al.* (claims 29-39). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached Monday, Tuesday, Thursday and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph. D. can be reached on 571-272-0928. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner